Remarks

Upon entry of the forgoing amendment, claims 1-40, 43, 47-67, 84-99, 102-115, 118-129, 132-133, and 136-138 are pending. Claims 44-46 are sought to be cancelled without prejudice or disclaimer thereto. Claims 1, 12, 14, 17, 19, 21, 23, 25, 28, 29, 32, 34, 37, 39, 43, 57, 61, 109, and 138 are amended to correct claim formalities as suggested by the Examiner. No new matter has been introduced by way of this amendment. Entry and consideration is respectfully requested.

Claim Objections

Claim 1 has been amended to delete the "a" in "a ten fold" as requested by the Examiner.

Claim 137 is amended to replace the comma at the end of the sentence with a period.

Claim 138 is amended to correct the spelling of "FSG" to "FSH."

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67, and 109 are rejected under 35 U.S.C. § 112, second paragraph for not clearly pointing out which subunit is being referred to in the claim since the claim now recites mutations in both the α- and β-subunits. Claim 1 is amended to clearly state "...wherein the modified β-subunit...," thereby rendering this rejection moot. Withdrawal is earnestly solicited.

Claims 12, 28, and 43 are rejected under 35 U.S.C. § 112, second paragraph, for reciting amino acid substitutions and not amino acids. These claims have been amended as suggested by the Examiner to refer to amino acids and not amino acid substitutions, thereby rendering this rejection moot. Withdrawal is earnestly solicited.

Claims 44-46 are rejected under 35 U.S.C. § 112, second paragraph, for not being clear which subunit the claimed nucleic acid encodes. Claims 44-46 are cancelled thereby rendering this rejection moot. Withdrawal is earnestly solicited.

Claim 109 is rejected under 35 U.S.C. § 112, second paragraph, for not being clear as to which subunits the claimed amino acid substitutions are in. Claim 109 has been amended as suggested by the Examiner to recite "of the α-subunit," thereby rendering this rejection moot. Withdrawal is earnestly solicited.

Rejections under 35 U.S.C. § 103

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67, 84-93, 95, 97-99, 104-109, 111, 113-115, 120-123, 127-129, and 136-138 are rejected under 35 U.S.C. § 103(a) as being obvious over Szkudlinski (WO 97/42322) or Szkudlinski (US 2002/0110909) in view of Schambye (US 2002/0127652). Applicants respectfully traverse.

Neither Szkudlinkski nor Schambye teach or suggest a modified FSH containing a modified α-subunit and a modified β-subunit wherein the modified β-subunit comprises at least one arginine at a position corresponding to positions 2, 4, 14, 63, 64, 67, and 69 of the β-subunit. As recognized by the Examiner on page 9 of the Office Action, Szkudlinski does not teach modifications in the FSH β-subunit as required by the claims. Schambye does not cure this defect.

Contrary to the Examiner's assertion, Schambye does not teach or suggest a modified FSH β-subunit with at least one arginine at positions 2, 4, 14, 63, 64, 67 or 69. As stated by the Examiner on page 9 of the Office Action, Schambye teaches an FSH β-subunit with lysine residues at, for example, residues 2, 4, 14, 63, 64, 67 and 69. The substitution of the lysine

residues in Schambye are made for the purpose of introducing amino acid residues comprising an attachment group for a non-polypeptide moiety to prolong the half-life of FSH. Thus, one of ordinary skill in the art would not have even thought of substituting arginine residues for the lysine residues of Schambye since the introduction of arginine would not have lead to the generation of better attachment residues for any non-polypeptide moiety since lysine is a much better attachment residue than arginine. Put another way, the problem to be solved in Schambye is quite different from that in the current application. As stated above, the goal in Schambye was to generate an FSH analog that had a longer half life and was more stable (*See* Schambye at Page 2, paragraph [0017]). The inventors of the current application, on the other hand, have solved the problem relating to potency and have generated FSH analogs that are at least about 10 fold more potent than wild type FSH (*See* current claim 1). Therefore, contrary to the Examiner's assertion, it would NOT have been obvious to substitute arginine at positions 2, 4, 64, 67 and 69 of the modified β-subunit of Schambye, because adding an arginine instead of a lysine would not lead to the introduction of glycosylation sites and therefore would not be expected to enhance stability of the β-subunit as was the aim of Schambye.

Furthermore, contrary to the Examiner's assertion, nowhere does Schambye teach a method for constructing "superactive analogs of human glycoprotein hormones." In fact, no where does Schambye even mention the term "superactive analog." The Examiner points to claim 79, and paragraphs [0012], [0025], [0077] and [0078] of Schambye in support of her assertion. Applicants respectfully point out that Schambye does not recite a claim 79. Furthermore, paragraph [0012] recites background attempts at improving stability of FSH, not activity. In fact, paragraph [0012] states "The resulting modified subunit is stated to have the biological activity of native FSH, but a prolonged circulating half life." Additionally, paragraph

[0025] does not support the Examiner's contention that Schambye teaches selecting superactive analogs, rather paragraph [0025] recites an aspect of the Schambye invention for methods of preparing a polypeptide or conjugate. Similarly, neither paragraph [0077] nor [0078] support the Examiner's assertion of Schambye teaching superactive analogs. Instead, paragraph [0077] teaches the removal or substitution of a lysine residue for the purposes of introducing an N-glycosylation site modification and paragraph [0078] teaches introduction of at least one O- or N-glycosylation site into the α- or β-subunit of human FSH. Nowhere do any of these paragraphs even mention arginine residues or increasing potency of FSH.

Additionally, contrary to the Examiner's assertion, Schambye does not teach that arginine would be an "appropriate substitution for lysine in the contemplated amino acid positions." The Examiner sites to paragraph [0120] to support her contention that the arginine would be an appropriate substitution for lysine in the contemplated amino acid positions. Applicants respectfully point out that paragraph [0120] of Schambye teaches the removal of wild type lysine residues in the β-subunit for the purposes of avoiding glycosylation of an internal lysine residue near the receptor binding site. (*See* paragraphs [0109], [0119] and [0120] of Schambye). Thus, as was explained by Applicants above, by substituting the lysine for an arginine, one is effectively removing a glycosylation site. Therefore, one of ordinary skill in the art would have most certainly not substituted an arginine for the lysines at positions 2, 4, 64, 67 and 69 of Schambye since adding a arginine instead of a lysine at these positions would not allow for the intended glycosylation of the FSH β-subunit.

Taken together, Szkudlinski does not teach or suggest modified FSH β-subunits with arginine substitutions at one or more positions corresponding to positions 2, 4, 14, 63, 64, 67 and

69 of SEQ ID NO:2 and Schambye does nothing to cure this defect. Withdrawal of this rejection is earnestly solicited.

Double Patenting Rejections

Claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67 and 136-138 are rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-45 of US 7,070,788 in view of Schambye. According to the Examiner, US 7,070,788 teaches the claimed modifications in the FSH α-subunit and Schambye teaches lysine modifications in the β-subunit and that, it would have been obvious to substitute the Schambye lysine substitutions with arginine and combine the mutated Schambye β-subunit to the mutated α-subunit of 7,070,788 to arrive at the currently claimed modified FSH. For the reasons discussed above for the 103(a) rejections, Applicants respectfully disagree and request withdrawal of this rejection.

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

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Respectfully submitted,
COOLEY LLP

By: _____
Alyson C. Fuller
Reg. No. 61,844

COOLEY LLP
ATTN: Patent Group
777 6th Street NW, Suite 1100
Washington, DC 20001
Tel: (202) 728-7129
Fax: (202) 842-7899